

Bone pain mechanism in osteoporosis: a narrative review

Consalvo Mattia¹
Flaminia Coluzzi¹
Ludovica Celidonio¹
Renato Vellucci²

¹ Department of Medical and Surgical Sciences and Biotechnologies, Unit of Anaesthesiology, Intensive care Medicine and Pain Therapy, Faculty of Pharmacy and Medicine, "Polo Pontino", "Sapienza" University of Rome, Italy

² Palliative Care and Pain Therapy Unit, University Hospital of Careggi, Florence, Italy

Address for correspondence:

Consalvo Mattia
Department of Medical and Surgical Sciences and Biotechnologies, Unit of Anaesthesiology, Intensive care Medicine and Pain Therapy
Faculty of Pharmacy and Medicine
"Polo Pontino", "Sapienza" University of Rome, Italy
E-mail: consalvo.mattia@uniroma1.it

Summary

Bone pain in elderly people dramatically affects their quality of life, with osteoporosis being the leading cause of skeletal related events. Peripheral and central mechanisms are involved in the pathogenesis of the nervous system sensitization. Osteoporosis in the elderly has been associated with increased density of bone sensory nerve fibers and their pathological modifications, together with an over-expression of nociceptors sensitized by the lowering pH due to the osteoclastic activity. The activation of N-methyl-D-aspartate (NMDA) receptors and the microglia, as a response to a range of pathological conditions, represent the leading cause of central sensitization. Unfortunately, osteoporosis is named the "silent thief" because it manifests with painful manifestation only when a fracture occurs. In the management of patients suffering from bone pain, both the nociceptive and the neuropathic component of chronic pain should be considered in the selection of the analgesic treatment.

KEY WORDS: bone; pain mechanism; osteoporosis; opioids.

Introduction

Managing bone pain is a frequent challenge for clinicians, mainly observed in elderly patients. Bone pain can dramatically worsen functional capacity and quality of life of affected people. Severe

chronic pain affects 19% of European adults; in Italy, this percentage reaches 26%. Osteoarthritis (OA) is the main cause of chronic bone pain (1), however most of these patients are affected by metabolic disorders, such as osteoporosis (OP) (1). Osteoporotic fractures, particularly in the hip, result in disability with reduction of performance, as measured by the activities of daily living (ADL), and are associated with increased nursing home and rehabilitation hospital admissions (2, 3). Severe bone pain caused by osteoporosis, when untreated or undertreated, can quickly lead to central sensitization (4); thus it can contribute to clinical manifestation of osteoporotic pain and to its chronicization (5, 6).

The aim of this review is to investigate the mechanisms of osteoporotic pain, focusing on peripheral and central mechanisms of sensitization.

Methods

We searched PubMed, EMBASE, and the Cochrane Database using the following search terms: "osteoporosis" or "metabolic bone disease" and "pain" or "chronic pain". Studies were included in the review if they were RCTs, review or guidelines; limits: English language, human adults.

Peripheral mechanisms of bone pain

Bone is not more considered an inanimate tissue, but is a widely innervated one; moreover bone innervation has a fundamental role in the regulation of physiological phenomena as the local blood flow and bone remodelling (7, 8). The adult skeleton is innervated largely by thinly myelinated, Tropomyosin Receptor Kinase A (TrkA)+ sensory nerve fibers (A-delta) and the peptide-rich Calcitonine-Gen Related Peptide (CGRP), and receives little if any innervation by the larger more rapidly conducting A-beta fibers or the TrkA-, unmyelinated peptide-poor C-fibers (9, 10).

It is important to underline that, whereas bone mass and strength decline with age, density of sensory nerve fibers in the tissue does not decline in older age, therefore the bone innervation "density" increases with age (10).

Previous studies have shown that sympathetic nerve fibers in bone can regulate bone destruction, bone formation, vasodilation, vasoconstriction, macrophage infiltration and bone progenitor cell function.

Thus, those nerve fibers have a central role in a great number of diseases progression in both cartilage (i.e. rheumatoid arthritis) and bone (i.e. osteoporosis - OP); for this reasons it is demonstrated that they play a significant role in the physiopathology of bone pain (11-14).

It is reasonable to assume that the sympatic nervous system and other mediators are involved in a complex network of interactions, resulting in an increased bone resorption and patchy OP in complex regional pain syndrome (CRPS) (15); in fact several trials are exploring a pharmacological blockade of the β -adrenergic system,

by using β -blockers, on post-menopausal OP (16, 17). However the argument about the influence of β -blockers on bone mass density seems to be endless and He et al. conclude that only definitive, randomized and controlled trials of β -blockers, with skeletal related events (SREs) as clinical endpoint, will be able to get solid evidence supporting the hypothesis that β -adrenergic system could contribute to postmenopausal bone health (15).

Moreover, following skeleton injury, sympathetic nerve fibers can modulate sensory nerve fibers function and this pathological interaction between sensory and sympathetic nerve fibers may play a role in CRPS (18).

During osteoclasts hyperactivity, transient receptor potential vanilloid 1 (TRPV1) and acid-sensing ion channel-3 (ASIC-3), which are acid sensing ions channels, are overexpressed by nociceptors on sensory neurons; and they are excited and sensitized by a decrease in pH (19, 20). It has been suggested that local acidosis, caused by production of extracellular protons, may also be involved in sensitizing the primary afferents in bone, through the activation of ASICs-3 (19). An imbalance between osteoblastic and osteoclastic activity is demonstrated in bone cancer but also in metabolic diseases such as OP, and this increased osteoclastic activity is associated with bone pain (20).

At our knowledge, there are no papers that studied the relationship between osteoclastic activity and osteoporotic pain, but it is well known that osteoclastic cells play a fundamental role in bone cancer pain. The increased osteoclast proliferation and activation observed in cancer-induced bone pain are connected to an increased production and release of Receptor Activator of Nuclear Factor K (RANK) ligand (RANK-L). The tumor interrupts the normal balance between RANK and RANK-L by increasing secretion of RANK-L from both cancer cells and T cells, thus accelerating bone degradation (21-24). The high affinity nerve growth factor (NGF) receptors Trk A may be expressed by skeleton sensory nerve fibers; these receptors mediate the multiple effects of NGF, including neuronal differentiation and survival (9, 25).

A significant increase in TrkA+ nerve fibers can be observed following skeleton injury or disease; moreover endogenous stromal cells as well as inflammatory and immune cells can produce NGF causing pathological alterations of bone innervation (26-28). Therefore several mechanisms contribute to generate and maintain pain in OP:

- increasing density of bone sensory nerve fibers in the elderly;
- sensory nerve fibers expressing nociceptors sensitized by the lowering pH (as observed during osteoclastic activity);
- bone sensory nerve fibers that undergo pathological modifications during bone pathological processes.

The periosteum receives the majority of sensory innervation of any other compartment of the skeleton.

In the periosteum, the A-delta and C-sensory nerve fibers are arranged in a fishnet-like pattern, which appears to be designed to act as a 'neural net' to detect mechanical injury or distortion of the underlying cortical bone (29).

In the cortical bone, both A-delta and C-fibers typically colocalise with blood vessels that run through the Haversian and Volkmann canals; however it is clear that the majority of blood vessels in these canals is not innervated by sensory nerve fibers. This may be one of the reasons why bone microfractures may not at least initially be perceived as painful (26). For this reason OP is named the "clinically silent thief", because pain is perceived only when pathological fractures occur, probably detected by mechanotransducers expressed by the A-delta and C-sensory fibers (26).

Moreover, regarding mechanoreceptors, we well know that those who transmit cutaneous pain sensation are both mechano-sensitive (CM) and mechano-insensitive (CMi) fibres, the last

showing a lower initial conduction velocity, more activity-dependent conduction velocity slowing, and more prominent post-spike supernormality. After sensitization with NGF, the electrical signal of CMi fibres changes towards a profile similar to that of CM fibres, influencing chronic pain states (30).

Finally, neuropeptides play an important role in the pathogenesis of OP, which may cause pain and influence the bone microstructure (31).

In particular, a number of neuropeptides, such as substance P (SP), CGRP, vasoactive intestinal peptide (VIP) and neuropeptide Y (NP-Y) are synthesized in sympathetic nerves and released from their peripheral terminals, which were found in the bone and periosteum tissue. These neuropeptides have been implicated in the regulation of local bone turnover in addition to nociception, inflammation, angiogenesis, and cellular proliferation. This indicates that neuropeptides may be modulators of bone metabolism, affect bone microstructure, and are involved with the pathogenesis of OA and OP (32).

Patients suffering from OA and OP present varying degrees of pain, although the mechanism is unclear. Xiao et al. (31) showed that VAS score, both in OA and OP patients, was positively correlated with several neuropeptides levels (SP, CGRP, VIP). These results implied that these peptides are involved in pain generation.

Central sensitization

Nociceptor inputs can trigger a prolonged increase in the excitability and synaptic efficacy of neurons in central nociceptive pathways, leading to a central sensitization.

The typical clinical manifestations of central sensitization are: pain hypersensitivity, dynamic tactile allodynia, secondary punctate or pressure hyperalgesia, and enhanced temporal summation.

This mechanism involves the activation of N-methyl-D-aspartate (NMDA) receptors and the release of SP, which amplifies pain, by causing the spinal neurons to be easily stimulated (6).

In particular, glutamate release by sensory afferent neurons acts on α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, when the impulse is acute and brief. However, if repetitive and high-frequency stimulus from C-fibres are received, amplification and prolongation of the response occurs, known as wind-up, through activation of the NMDA receptors. Normally, NMDA receptors are blocked by the ion Mg^{2+} , however, under continuous stimulation this "cork" is removed. The removal of the Mg^{2+} block is probably facilitated by the co-release of SP and CGRP from C-fibres (33, 34). This enhanced NMDA receptors activation plays a role in inflammatory and neuropathic pain states (35, 36) and results in the activation and exacerbation of secondary hyperalgesia. They also initiate translational changes of the second-order neurones, which might be a crucial link in the pathogenesis of chronic pain (37, 38).

Moreover, the spinal cord is an important pain processing crossroad receiving input from peripheral neurones, inter-neurones, astrocytes and microglia, and descending modulatory inhibitory pathways.

Neuroplasticity, or the physical remodelling of neuronal cytoarchitecture, occurs shortly after the onset of persistent acute pain and leads to the transition from acute pain into a chronic pain state. As a result of a peripheral lesion that persistently generates pain impulses to the spinal cord, inhibitory inter-neurones, responsible for modulating painful nerve transmission impulses, eventually die. Furthermore, glial cells may contribute to the remodelling of neuronal synapses, in order to intensify nociceptive transmission. These pain-transmitting neurones become more sensitive, react more intensely to painful stimuli, and more connections grow

up within the CNS (39).

As mentioned above, spinal glial activation is now considered an important component in the development and maintenance of central sensitization (40):

- The microglia seems to respond to a range of pathological conditions such as ischemia, infections and mechanical insults, modifying itself in such a way that the risk of complicating pain with a neuropathic component is incremented;

- The release of proinflammatory mediators leads to an activation of glia, which tends to self-renew and causes excessive stimulation of the spinal cord gray matter, producing sensory disturbances typical of the neurological damage. If peripheral sensitization and neuronal sensitivity long-term potentiation in the dorsal horn of the spinal cord occur, it is very likely the transition from an acute to a chronic process. Changes in nociceptor function can be broadly divided into modulation or modification. Modulation represents reversible changes in the excitability of primary sensory and central neurones mediated by post-translational modifications of receptors and ion channels by activation of intracellular signal-transduction cascades. Modification represents long lasting alterations in the expression of transmitters, receptors, and ion channels or in the structure, connectivity, and survival of neurones; therefore the cytoarchitecture is modified altering normal stimulus-response characteristics (41).

Modification is the more plausible link explaining the transition from acute to chronic pain (42). The described changes in upregulation of dynorphin, CGRP and SP in the spinal cord, astrocyte hypertrophy and microglial activation (43) explain phenomena such as increased skeletal pain-related behaviours, enhanced phosphorylation of NMDA receptor NR-1 subunits, increased expression of NR2B (an NMDA receptor subunit), and interleukin-1 β released from glial cells. Moreover it is important to underline that injury to the skeleton seems to be much more effective in inducing central sensitization as compared to injury to skin or muscle (44).

Unfortunately, nowadays our knowledge of the specific mechanisms that drive central sensitization in chronic skeletal pain is limited, but we hope that in the future we can understand these changes that generate and maintain central sensitization, in order to design targeted therapies to treat the central sensitization.

Clinical aspects

OP, the “silent thief”, causes few symptoms for long time. It steals for years calcium from bone and then manifests with painful manifestation only when a fracture occurs.

The most frequent is the vertebral compression fracture in the spine. Most cases occur in the thoraco-lumbar tract and have usually an insidious onset (45, 46). Pain can be sudden and severe, especially in the lower back, so that movements are difficult or impossible.

Multiple fractures may lead to progressive loss of stature and continuous contraction of the paraspinal musculature to maintain posture. It has been hypothesized that fractures occur because of an increased load on the spine cause by contraction of paraspinal muscles (47) and may produce only low-grade back pain, only rarely associated with neurologic deficits.

Fatigued muscles and pain may continue even after the original compression fractures have healed (48). There is a complexity and mix of inflammatory and neuropathic components and this should represent the basis for the choice of the clinic treatment of pain.

In this situation, often a single agent is not enough and multiple mechanisms of action provide a rational basis for the use of com-

bination therapy. In bone cancer pain, dual therapy with mu opioid receptor agonists and noradrenaline reuptake inhibitors (MOR/NRI) was shown to be effective in reducing neuropathic component of mixed pain (49). A balanced and early multimodal pain therapy including opioids, as necessary, even in case of acute pain, improve the functional capacity of patients and helps to prevent neurological alterations, which seem to contribute in a significant way in causing irreversible pain chronic syndromes (50).

When treating OP related pain opioid-associated androgen deficiency (OPIAD) syndrome should be considered, as this could be related with an increased risk of OP; thus, despite that standards have not been established for monitoring and treating opioid-induced hypogonadism or hypoadrenalism, all patients chronically taking opioids (particularly at doses >100 mg morphine daily) should be monitored for the early detection of hormonal impairment and low bone mass density (51).

Conclusions

Bone pain caused by OP is still a challenge for physicians. The initially silent thief becomes clinically relevant and painful only when fractures occur. Several important peripheral mechanisms are involved in this pathological process, such as:

- sensory nerve fibers expressing TRPV1 and ASIC-3 are sensitized by lowering of pH during osteoclastic activity;
- bone sensory nerve fibers undergo pathological modifications, such the expression of Trk A receptors;
- a number of neuropeptides, such as SP, CGRP, VIP and NPY, synthesized in sympathetic nerve fibers and released from their peripheral terminals, are found in the bone and periosteum tissue during osteoporosis;
- the increasing density of bone sensory nerve fibers in the elderly associated with a decreased bone mass density amplifies these mechanisms.

These new findings should be considered when a therapeutic program is established to treat OP pain, in order to avoid pain under-treatment and central sensitization.

Financial disclosure

All Authors declare that they have no conflicts of interest.

References

1. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain*. 2006 May;10(4):287-333.
2. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. *Lancet*. 2002;359:1761-1767.
3. Aizer J, Bolster MB. Fracture liaison services: promoting enhanced bone healthcare. *Curr Rheumatol Rep*. 2014;16:455.
4. Mattia C, Di Bussolo E, Coluzzi F. Non-analgesic effects of opioids: the interaction of opioids with bone and joints. *Curr Pharm Des*. 2012;18(37):6005-9.
5. Smart KM, Blake C, Staines A, Doody C. The Discriminative Validity of “Nociceptive,” “Peripheral Neuropathic,” and “Central Sensitization” as Mechanisms- based Classifications of Musculoskeletal Pain. *Clin J Pain*. 2011;27(8).
6. Haviv B, Bronak S, Thein R. The complexity of Pain around the Knee in Patients with osteoarthritis. *IMAJ*. 2013;15.
7. Bjurholm A, Krif. Icbjergs A, Terenius L, Goldstein M, Schultzberg M. Neuropeptide Y-, tyrosine hydroxylase- and vasoactive intestinal polypeptide-immunoreactive nerves in bone and surrounding tissues. *J Auton Nerv Syst*. 1988;25:119-125.

8. Davidovitch Z, Nicolay O, Ngan PW, Shanfeld JL. Neurotransmitters, cytochines, and die control of alveolar bone remodelling in orthodontics. *Dent Clin North Am.* 1988;32:411-435.
9. Zylka MJ, Rice FL, Anderson DJ. Topographically distinct epidermal nociceptive circuits revealed by axonal tracers targeted to Mrgrp. *Neuron.* 2005 Jan 6;45(1):17-25.
10. Jimenez-Andrade JM, Mantyh WG, Bloom AP, Freeman KT, Ghilardi JR, Kuskowski MA, Mantyh PW. The effect of aging on the density of the sensory nerve fiber innervation of bone and acute skeletal pain. *Neurobiol Aging.* 2010;33:921-932.
11. Asmus SE, Parsons S, Landis SC. Developmental changes in the transmitter properties of sympathetic neurons that innervate the periosteum. *The Journal of neuroscience: the official journal of the Society for Neuroscience.* 2000;20:1495-1504.
12. Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES. The sympathetic nerve-an integrative interface between two supersystems: the brain and the immune system. *Pharmacological reviews.* 2000;52:595-638.
13. Bataille C, Mauprivez C, Hay E, Baroukh B, Brun A, Chaussain C, Marie PJ, Saffar JL, Cherruau M. Different sympathetic pathways control the metabolism of distinct bone envelopes. *Bone.* 2012;50:1162-1172.
14. Eimar H, Tamimi I, Murshed M, Tamimi F. Cholinergic regulation of bone. *Journal of musculoskeletal & neuronal interactions.* 2013;13:124-132.
15. He JY, Jiang LS, Dai LY. The roles of the sympathetic nervous system in osteoporotic diseases: A review of experimental and clinical studies. *Ageing Research Reviews.* 2011;10:253-263.
16. Bonnet N, Laroche N, Vico L, Dolleas E, Benhamou CL, Courteix D, 2006. Dose effects of propranolol on cancellous and cortical bone in ovariectomized adult rats. *J Pharmacol Exp Ther.* 2006;318:1118-1127.
17. Bonnet N, Gadois C, McCloskey E, Lemineur G, Lespessailles E, Courteix D, Benhamou CL. Protective effect of blockers in postmenopausal women: influence on fractures, bone density, micro and macroarchitecture. *Bone.* 2007;40:1209-1216.
18. Pepper A, Li W, Kingery WS, Angst MS, Curtin CM, Clark JD. Changes resembling complex regional pain syndrome following surgery and immobilization. *The Journal of Pain: official journal of the American Pain Society.* 2013;14:516-524.
19. Julius D, Basbaum AI. Molecular mechanisms of nociception. *Nature.* 2001;413:203-10.
20. Nagae M, Hiraga T, Wakabayashi H, Wang L, Iwata K, Yoneda T. Osteoclasts play a part in pain due to the inflammation adjacent to bone. *Bone.* 2006 Nov;39(5):1107-15.
21. Urch C. The pathophysiology of cancer induced bone pain: Current understanding. *Palliat Med.* 2004;18:267-274.
22. Clohisy DR, Perkins SL, Ramnaraine ML. Review of cellular mechanisms of tumor osteolysis. *Clin Orthop Relat Res.* 2000;373:104-114.
23. Coluzzi F, Di Bussolo E, Mandatori I, Mattia C. Bone metastatic disease: taking aim at new therapeutic targets. *Curr Med Chem.* 2011;18(20):3093-115.
24. Coluzzi F, Mandatori I, Mattia C. Emerging therapies in metastatic bone pain. *Expert Opin Emerg Drugs.* 2011 Sep;16(3):441-58.
25. Jimenez-Andrade JM, Mantyh WG, Bloom AP, Xu H, Ferng AS, Dussor G, Vanderah TW, Mantyh PW. A phenotypically restricted set of primary afferent nerve fibers innervate the bone versus skin: Therapeutic opportunity for treating skeletal pain. *Bone.* 2011;46:523-529.
26. Mantyh PW. The neurobiology of skeletal pain. *European Journal of Neuroscience.* 2014;39:508-519.
27. Skaper SD, Pollock M, Facci L. Mast cells differentially express and release active high molecular weight neurotrophins. *Brain Res Mol Brain Res.* 2001;97:177-185.
28. Ehrhard PB, Erb P, Graumann U, Otten U. Expression of nerve growth factor and nerve growth factor receptor tyrosine kinase Trk in activated CD4+ positive T-cell clones. *Proc Natl Acad Sci USA.* 1993;90:10984-10988.
29. Martin CD, Jimenez-Andrade JM, Ghilardi JR, Mantyh PW. Organization of a unique net-like meshwork of CGRP+ sensory fibers in the mouse periosteum: Implications for the generation and maintenance of bone fracture pain. *Neuroscience letters.* 2007;427:148-152.
30. Petersson ME, Obreja O, Lampert A, Carr RW, Schmelz M, Fransén E. Differential axonal conduction patterns of mechano-sensitive and mechano-insensitive nociceptors-a combined experimental and modelling study. *PLoS One.* 2014 Aug 19;9(8).
31. Xiao J, Yu W, Wang X, Wang B, Chen J, Liu Y, Li Z. Correlation between neuropeptide distribution, cancellous bone microstructure and joint pain in postmenopausal women with osteoarthritis and osteoporosis. *Neuropeptides.* 2015 Dec 8.
32. Abdelaziz DM, Abdullah S, Magnussen C, Ribeiro-da-Silva A, Komarova SV, Rauch F, Stone LS. Behavioral signs of pain and functional impairment in a mouse model of osteogenesis imperfecta. *Bone.* 2015 Dec;81:400-6.
33. Suzuki R, Hunt SP, Dickenson AH. The coding of noxious mechanical and thermal stimuli of deep dorsal horn neurones is attenuated in NK1 knockout mice. *Neuropharmacology.* 2003;45:1093-100.
34. Khasabov SG, Rogers SD, Ghilardi JR, Peters CM, Mantyh PW, Simone DA. Spinal neurons that possess the substance P receptor are required for the development of central sensitization. *J Neurosci.* 2002;22:9086-98.
35. Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain.* 1999;83:389-400.
36. Price DD, Mao J, Frenk H, Mayer DJ. The N-methyl-D-aspartate receptor antagonist dextromethorphan selectively reduces temporal summation of second pain in man. *Pain.* 1994;59:165.
37. Eide PK. Wind-up and the NMDA receptor complex from a clinical perspective. *Eur J Pain.* 2000;4:5-15.
38. Bennett GJ. Update on the neurophysiology of pain transmission and modulation: focus on the NMDA-receptor. *J Pain Symptom Manage.* 2000;19:S2-6.
39. Torebjork HE, Lundberg LE, LaMotte RH. Central changes in processing of mechanoreceptive input in capsaicin-induced secondary hyperalgesia in humans. *J Physiol.* 1992;448:765-80.
40. Wang W, Huang J, Wei Y, Wang Y, Wu S, Li Y. Crosstalk between Spinal Astrocytes and Neurons in Nerve Injury-Induced Neuropathic Pain. *PLoS One.* 2009;4(9):e6973.
41. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. *Science.* 2000;288:1765-9.
42. Voscopoulos C, Lema M. When does acute pain become chronic? *British Journal of Anaesthesia.* 2010;105 Suppl;1:i69-85.
43. Ren K, Dubner R. Neuron-glia crosstalk gets serious: role in pain hypersensitivity. *Current opinion in anaesthesiology.* 2008;21:570-579.
44. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. *Nature.* 1983;306:686-688.
45. Robinson Y, Heyde CE, Försth P, Olerud C. Kyphoplasty in osteoporotic vertebral compression fractures guidelines and technical considerations. *J Orthop Surg Res.* 2011 Aug 19;6:43.
46. Nevitt MC, Ettlinger B, Black DM, Stone K, Jamal SA, Ensrud K, Segal M, Genant HK, Cummings SR. The association of radiographically detected vertebral fractures with back pain and function: a prospective study. *Ann Intern Med.* 1998 May 15;128(10):793-800.
47. Kim DH, Vaccaro AR. Osteoporotic compression fractures of the spine; current options and considerations for treatment. *Spine J.* 2006 Sep-Oct;6(5):479-87.
48. Wu SS, Lachmann E, Nagler W. Current medical, rehabilitation, and surgical management of vertebral compression fractures. *J Womens Health (Larchmt).* 2003 Jan-Feb;12(1):17-26.
49. Coluzzi F, Raffa RB, Pergolizzi J, Rocco A, Locarini P, Cenfra N, Cimino G, Mattia C. Tapentadol prolonged release for patients with multiple myeloma suffering from moderate-to-severe cancer pain due to bone disease. *J Pain Res.* 2015 May 8;8:229-38.
50. Vellucci R, Mediatl RD, Ballerini G. Use of opioids for treatment of osteoporotic pain. *Clin Cases Miner Bone Metab.* 2014 Sep;11(3):173-6.
51. Coluzzi F, Pergolizzi J, Raffa RB, Mattia C. The unsolved case of "bone-impairing analgesics": the endocrine effects of opioids on bone metabolism. *Therapeutics and Clinical Risk Management.* 2015;11:515-523.